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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUI, SAN MING R	
ART UNIT	**PAPER NUMBER**
1617	24

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/715,478	ALLISON ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendments filed September 10, 2003 have been entered.

The addition of claims 11-20 in Applicant's amendments filed September 10, 2003 is acknowledged.

Examiner wants to thank you the Applicant in pointing out that claims 7 and 8, drawn to the method of treating, reducing, and inhibiting restenosis or intimal hyperplasia employing green porphyrin, such as BPD-MA and A-EA6 is considered free of prior art. Therefore, rejection under 35 USC 103(a) of claims 7 and 8 is withdrawn.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 and 12-19 of U.S. Patent No. 09/716,022 (herein after referred as '022). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The conflicting claims in '022 recited the method of treating blood vessel grafts, including arteries and veins graft with the instant photodynamic therapeutic agents along with irradiation to prevent, treat, reduce or inhibit restenosis or intimal hyperplasia.

The claims in '022 do not teach that 1) the specific dosing range ($0.25 - 25 J/cm^2$) as recited in the instant claims; 2) the instant claims employ the photodynamic agents within a specific time of angioplasty procedure; 3) the application of a stent; and 4) the timing of administration steps.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the specific herein claimed dosage regimen (i.e., the specific dosing range and timing of photodynamic therapy) and the application of a stent in the method of '022.

One of ordinary skill in the art would have been motivated to employ the specific herein claimed dosage regimen and the application of a stent in the method of '022 because optimization of dosing regimen is obvious as being within the skilled artisan. Furthermore, angioplasty is a common procedure employed to treat restenosis or intimal hyperplasia in artery graft, which is commonly used in coronary bypass graft procedure. In addition, employing the stent with angioplasty in order to prevent the abrupt closure of the blood vessel, which helps to maintain the blood flow and prevent further myocardial infarction would be obvious (See Harrison, a textbook reference of record one of skilled artisan is charged to have possession).

Response to arguments

Applicant's arguments filed September 10, 2003 averring no motivation being provided in the prior art to combine angioplasty with photodynamic therapy together to treat restenosis have been considered, but are not found persuasive. Angioplasty is commonly used to treat narrowing of coronary blood vessel (stenosis), please see Harrison (a textbook reference of record that one of skilled artisan is charged to have possession). Photodynamic therapy of '022 is also known to be useful as a treatment for restenosis. Absent evidence to the contrary, concomitantly using both agents, which they are known to be useful as stenosis treating agent individually, for the treatment of stenosis would be *prima facie* obvious (See *In re Kerkhoven* 205 USPQ 1069).

Applicant's arguments filed September 10, 2003 averring no motivation being provided in the prior art to employ the method of '022 in the energy dosage herein claimed to treat restenosis have been considered, but are found persuasive. Examiner notes that without showing the criticality of the herein claimed range of energy dosage, the optimization of photo energy in photodynamic therapy is merely an adjustment of the energy dosage, which is obvious as being within the purview of skilled artisan.

Applicant's arguments filed September 10, 2003 averring not "all vascular grafts necessarily require angioplasty, and so no suggestion in the claims of the patent or any other source presented in the statement of the rejection to consider modifying the claims of the patent of use in combination with angioplasty" have been considered, but are not found persuasive. Angioplasty is not necessarily required for all vascular grafts. That may be true; however, it does not render the invention unobvious. Consider the

following example: Aspirin may not be required for all patients having headaches, but it does not mean that aspirin is not effective in treating headache. The crux of the rejection is based on the holding of the case *In re kerkhoven* that combining two agents, which are known to be useful for one purpose individually, into a combination seful for the very same purpose is obvious, absent evidence to the contrary.

Applicant's arguments filed September 10, 2003 in regard to *In re Baird, In re Deuel, In re Jones, and In re Bell* have been considered, but are not found persuasive. The instant case distinguishes from the situations of *Baird, Deuel, Jones,* and *Bell* because the four cases are concerning the picking and choosing from a very broad genus. However, this is not the crux of the instant rejection. In the prior art, it is known that both photodynamic therapy and angioplasty as effective in treating the narrowing of blood vessel (i.e., stenosis or restenosis). Therefore, absent evidence to the contrary, concomitantly using both agents, which they are known to be useful as stenosis treating agent individually, for the treatment of stenosis would be *prima facie* obvious (See *In re Kerkhoven* 205 USPQ 1069).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

The claims herein are very broad. As Applicant's points out in the reply filed February 10, 2003, page 4, second paragraph, the term prevent would encompass every degree of prevention, which includes absolute prevention. In the instant case, the specification fails to provide guidance as to how one skilled in the art would go about preventing restenosis or IH or how the arteries could be kept from being susceptible to these pathogenic changes ever again. Nor is there any guidance provided as to a

specific protocol to be utilized in order to prove the efficacy of the presently claimed method in preventing restenosis or IH. It is well known in the art, as evidenced by the articles provided through the IDS received October 1, 2001 and March 19, 2002, that absolute prevention of restenosis or IH is not likely. The art is focus on how to reduce the degree of or treat the already existed restenosis or IH. It is unclear how one of skilled artisan would be able to absolutely prevent restenosis or IH. Therefore, the quantity of experimentation would be enormously large for determining an embodiment to achieve the envisioned absolute preventive effect. Moreover, it is highly unlikely and unpredictable, if not nearly impossible, that after applying the herein claimed method once, there will not be any restenosis or IH occur ever again (i.e., absolute prevention) in the site of application. Examiner notes that Vincent et al., reference of record in the previous Office action, page 76, second paragraph, teaches that "intimal damage by virtually any means may induce a profliferative response." Furthermore, there is no working example disclosed in the specification in regard to the prevention of restenosis or IH. The burden of enabling the prevention of restenosis or intimal hyperplasia (IH) (i.e. the need for additional testing) is greater than that of enabling a treatment for restenosis or IH. The specification fails to enable one of ordinary skill in the art to practice and use the methods of instant claims 1-10. Absent such information or guidance, one of skilled artisan would be required to perform undue experimentation in order to practice the herein claimed method of preventing restenosis or IH.

Response to arguments

Applicant's arguments averring no proof or objective truth being provided by the Examiner have been considered, but are not found persuasive. Objective truth was cited. Please see articles provided through the IDS received October 1, 2001 and March 19, 2002 and Vincent et al., reference of record in the previous Office action, page 76, second paragraph, which teaches "intimal damage by virtually any means may induce a profliferative response." Such intimal damage would include the photodynamic therapy on the intimal wall tissue, which would be expected to induce, not reduce, proliferative response.

Applicant's arguments filed September 10, 2003 averring inoperative embodiments will not necessarily render the claim non-enabled have been considered, but are not found persuasive. Applicant further remarks if "absolute prevention" is not known in the art, there is no deficiency of enablement in the instant claims. The arguments and remarks have been considered, but are not found persuasive. Please note that there are four embodiments recited in the claims: 1) treat, 2) reduce, 3) inhibit, and 4) prevent the restenosis or IH. In the instant case, one out of four embodiments is inoperative. The claim is drawn to a method of preventing restenosis or IH employing photodynamic therapy with angioplasty. Given the broadest interpretation of the claims, it encompasses "absolute prevention". In order to determine whether "prevention" of the restenosis or IH is operative or not, undue experimentation is required. Therefore, the claims are still non-enalbed.

Applicant's arguments filed September 10, 2003 in regard to item 2) in page 11 have been considered, but are not found persuasive. It is known in the art as to how to determine the efficacy of the methods of preventing restenosis. However, it is not the issue in the instant case. The issue is whether the instant specification enable one skilled of artisan to practice the herein claimed invention without undue experimentation. As discussed above, because of the unpredictability and lack of guidance and working examples, undue experimentation would be required in order to practice the invention. It is note that Figures 1 and 2 showing the decrease in intimal thickness. However, prevention is not to decrease the intimal thickness. Decreasing the intimal thickness is considered as "reducing", "inhibiting", or "treating", but not preventing.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-6 and 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vincent'362 (US Patent 5,422,362, reference of record) in view Gonschlor et al. (Photochemistry and Photobiology, 1996; 64(5):758-763 from the IDS received October 5, 2001) and Harrison (Harrison's Principle of Internal Medicine, 13h ed., 1994, page 986, published by McGraw Hill).

Vincent'362 teaches Sobeh using Photofrin II, also known as porfimer sodium, in the concentration of 2μg/ml, to treat restenosis with light energy of greater than 3 J/cm^2. Such treatment results in the destruction of over 80% of smooth muscle cells (See col. 2, line 40-57). Vincent'362 teaches Dartsch using Photofrin II to markedly reduce plaque-derived smooth muscle cells without totally destroy the normal viable cells (See col. 2, line 12-39). Vincent'362 teaches the energy used in the Dartsch's experiment as 1.2J/cm^2 (see col. 2, line 34). Vincent'362 teaches Eton et al. using Photofrin II in rabbit model underwent standardized intimal injury to both common carotid arteries and balloon catheter (See col. 3, lines 6-22). Vincent'362 also teaches Eton et al. reported that Photofrin II and irradiation significantly improve the ratios of the area of IH to that enclosed by the internal elastic lamina (See col. 3, lines 15-22).

Vincent'362 does not expressly teach the injury is accompanied by angioplasty procedure using a stent. Vincent'362 does not expressly teach the timing between the application of the photosensitive agents and the irradiation as within 15 minutes or 5 minutes of administration step.

Gonschlor et al. teaches the use of photofrin, also known as profimer sodium, and irradiation in reducing intimal hyperplasia (See abstract). Gonschlor et al. teaches

that radiation source was employed immediately after the photosensitizing agent (See page 759, col. 1, Laser light application). Gonschlor et al. teaches that the injury was followed by the application of the photosensitizer and light source (See page 749, col. 1, first paragraph).

Harrison teaches that a stent can be used with angioplasty in order to prevent the abrupt closure of the blood vessel, which helps to maintain the blood flow and prevent further myocardial infarction (see page 986, col. 2, Second paragraph, last five lines).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ sodium profimer and irridiation together to treat and reduce IH or restenosis associated with angioplasty, where the angioplasty procedure may be involved with the use of a stent.

One of ordinary skill in the art would have been motivated to employ sodium profimer and irridiation together to treat and reduce IH or restenosis associated with angioplasty, where the angioplasty procedure may be involved with the use of a stent. According to three different studies disclosed in Vincent'362, sodium profimer is shown to be effective, when using with irradiaton, to treat or reduce IH in human stenosis cells, or in animal models. It is also known in the art that the timing of applying irradiation as immediately following the application of sodium profimer. Therefore, applying the irradiation source as recited herein would be reasonably expected to be effective in treating or reducing IH. Furthermore, it is known that stent is commonly used with angioplasty procedure in order to prevent abrupt collapse of blood vessel and at the same time maintaining blood flow to prevent myocardial infarction. Therefore, the

method of employing sodium profimer to reduce or treat IH associated with angioplasty, regardless of the employment of stent or not, would be reasonably expected to be effective, absent evidence to the contrary.

Response to arguments

Applicant's arguments filed September 10, 2003 averring Vincent not being pertinent to the instant invention since the treatment of cells culture as not the same as treating restenosis or IH in a blood vessel that undergoes angioplasty have been considered, but are not found persuasive. Although the treatment of cell cultures as not the same as treating restenosis or IH in a blood vessel that undergoes angioplasty, this is not the standard of obviousness rejection. It is a common practice in the pharmaceutical field to use non-human model to serve as a predictor of whether the agent will be successful or not in clinical trials. Therefore, the reasonable expectation of success is present in non-human study that shows therapeutic efficacy.

Applicant's arguments filed September 10, 2003 in regard to Eton's teachings have been considered, but are not found persuasive. Attention is directed to the treatment groups III and IV of Table 1 in Eton, page 560. Treatment with Photofrin only is clearly effective as compared to the control group [emphasis added]. Treatment with Photofrin and laser together is clearly better than treatment with either Photofrin alone or laser alone. Actually, Eton does not indicate that Photofrin is not at all effective. Examiner notes that photodynamic therapy involves in the application of the photosensitizer followed by energy activation. In Eton, the photosensitizer is Phtofrin,

and laser is to activate the compound so that Photofrin becomes more potent. Applicant's remarks stating that Photofrin "may be effective" against IH are not relevant to the basis of rejection. When using Photofrin alone without energy activation, it may be effective. But when it is used with energy activation, it is clearly effective. Examiner notes that the instant claims are drawn to a method of treating, reducing, inhibiting restenosis or IH with a photosensitizer and an energy source.

Applicant's arguments filed September 10, 2003 with regard to Gonschlor's teachings that the results cannot be directly extrapolated to use in human restenosis have been considered, but are not found persuasive. The results cannot be extrapolated to human restenosis because the arteries are nondiseased. Examiner notes that when viewing Gonschlor alone, it *may not* be as sufficient to motivate one of ordinary skill in the art to employ Photofrin and photodynamic therapy in treating IH or restenosis. However, taking all the references as a whole, one of ordinary skill in the art would have been motivated to employ Photofrin with energy in treating restenosis or IH.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (703) 305-1002. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

San-ming Hui
Patent Examiner
Art Unit 1617

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER

12/11/03